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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,494	ZUGICH ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *5-8,10,15 and 17-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 9, 11-14 and 16* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 12/4/03 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-4, 9 and 11-16), and species of SEQ ID NO: 12 from gp75 in Applicant's amendment filed 2/27/03.

Claims 1-4, 9 and 11-14 read on the elected species, SEQ ID NO: 12.

Upon consideration of a search, since SEQ ID NO: 12 appears to be free of the prior art, the search has been extended to include SEQ ID NO: 10 recited in claim 16.

Claims 1-4, 9, 11-14 and 16 are currently being examined.

3. With respect to Applicant's remarks on page 6 of the said amendment at the third paragraph, claim 10 is not considered drawn to a different invention than the claim it depends upon; it is considered drawn to the invention of Group II which contains base claim 1. Claim 1 was inadvertently left out of Group III, which contains claims 5 and 6. With regard to the species restriction applied to claim 15 the following applies. PCT Rule 13.2 provides that unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features, meaning those technical features that define a contribution which each of the inventions considered as a whole makes over the prior art. No special technical feature exists as enunciated in Paper No. 11 mailed 10/02/02. In addition, the peptides recited in claim 15 are not related to the elected species gp75 peptide TAYRYHLL (SEQ ID NO: 12) because they have different primary structures and because they elicit different CTL responses to different proteins.

4. For the purpose of prior art rejections, the filing date of the instant claims 2 and 4 is deemed to be the filing date of PCT/US99/13146, i.e. 6/11/99, as the parent applications do not support the claimed limitations of the instant application. The limitation "each consist of from 8 to 14 amino acids " is only disclosed in PCT application.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 2, 9, 11 and 12 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/29193, IDS reference) as evidenced by Overwijk et al (J. Exp. Med. 188(2) 277-286, 1998, IDS reference).

WO 95/29193 teaches a method of inducing an immune response by administering heteroclitic peptides from tumor antigens, including gp100, altered to improve peptide MHC class I (including HLA-A2.1) binding affinity and to render the peptide capable of inducing an immune response (i.e., "immune recognition domain binds to a cytotoxic T cell") whereas it had not been immunogenic prior to alteration (especially introduction and last paragraph on page 104). The peptides are 8 amino acid residues in length, i.e., "from 8 to 14 amino acids". WO 95/29193 teaches that some of the wild-type peptides induce a partial response or no response at all as measured by recognition by HLA-A2 restricted TIL, i.e., are "weakly immunogenic" (entire article, especially Tables, Table 11). The peptides taught by WO 95/29193 are "from 8 to 14 amino acids" in length.

Overwijk et al teach many tumor-associated antigens such as gp100 are poorly immunogenic tissue differentiation antigens, i.e., they are weakly immunogenic (especially page 277). Overwijk et al teaches gp100 is expressed by normal melanocytes and the majority of malignant melanomas and that CTL with reactivity to gp100 have been detected in patients with metastatic melanoma (especially column 1 on page 278). Claim 12 is included in this rejection because it is an inherent property of gp100 that it is expressed in normal and tumor tissues.

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

It is Applicant's position beginning on page 7 of the said amendment that the claims as amended require that the target peptide as a whole be non-immunogenic or only weakly immunogenic, and that the rejection does not support this position. It is the Applicant's further position with regard to evidentiary reference Overwijk et al that gp100 does not fall within the scope of the present claims because a detectable CTL response to gp100 is observed, that gp100 is the target antigen.

It is the Examiner's position that the peptides taught by WO 95/29193 in Table 11 are recognized by some TIL from some patients and not by other TIL from other patients. WO 95/29193 teaches that the "G9-209 and G9-280 are not high affinity binders, but by changing the amino acid at the first, second, third or ninth positions which are important for HLA-A2 binding to the peptide, but less important for recognition by T-cell receptors,

artificial peptides which can bind to HLA-A2.1 with higher affinity and still be recognized by natural epitope specific T-cells may be generated" (especially page 104 at paragraph 1). In addition, WO 95/29193 teaches (as enunciated supra) on page 104 at the last paragraph that "Other peptides which were not recognized by the particular T-cells used in our study, but have higher binding affinity to HLA-A2.1 may induce a different set of T-cells capable of recognizing the original melanoma epitopes in in vitro or in vivo. These modified peptides may be used for induction of anti-melanoma T-cells in vitro and immunization of patients for the treatment of patients with melanoma or for the prevention of melanoma." It is the Examiner's further position with regard to Applicant's comments on Overwijk et al, that the present claims are drawn to a "target peptide that is non-immunogenic or weakly immunogenic in a mammalian subject" and that the "therapeutic antigen is derived from the target peptide such that the MHC-binding portion binds to MHC with a greater affinity than the target peptide without material alteration of the immune-recognition portion", and as such, the target peptide is a peptide from gp100 that is non-immunogenic or weakly immunogenic, not the gp100 protein. Also, Overwijk et al teach unresponsiveness to gp100 in mice, i.e., a mammalian subject, is broken by using a peptide homologue with higher affinity for MHC class I (especially last paragraph of article).

7. Claims 1, 2, and 9 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lipford et al (Immunology 84(2), 1995, 298-303, IDS reference).

Lipford et al teach a method of inducing an immune response by administering a heteroclitic peptide YIFAFRDL which was altered from HPV E6 peptide YDFAFRDL at position 2 to improve peptide MHC class I H-2Kb binding affinity, and to render it capable of inducing an immune response (i.e., "immune recognition domain binds to a cytotoxic T cell") whereas it had not been immunogenic prior to alteration (especially introduction and last paragraph on page 302). The peptides are 8 amino acid residues in length, i.e., "from 8 to 14 amino acids".

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

It is Applicant's position beginning on page 7 of the said amendment that the Lipford et al reference does not address whether HPV antigen E6 itself is a target antigen within the scope of the present claims, i.e., one which is weakly immunogenic or non-immunogenic.

It is the Examiner's position that the claims do not recite wherein the target antigen is non-immunogenic or weakly immunogenic, but rather that a target peptide is non-immunogenic or weakly immunogenic.

8. Claim 2 stands rejected under 35 U.S.C. 102(a) as being anticipated by Dyall et al (J. Exp. Med 188(9), 1553-1561, 11/2/98, IDS reference).

Dyall et al teach a method for inducing a cellular immune response to a heteroclitic peptide SSIEFARL (i.e., the therapeutic antigen) (hsV-8), which is a variant of peptide SEIEFARL (i.e., the target antigen) which binds poorly to the murine class I MHC molecule H-2Kb and which due to poor binding cannot elicit a CTL response in Kb-bearing B6 mice (especially paragraph spanning columns 1 and 2 on page 1555) and also to a heteroclitic variant TAYRYHLL of peptide TWHRYHLL from gp75 which displayed poor binding similar to the SEIEFARL peptide (especially page 1557). Both heteroclitic peptides bound with greater affinity than the target peptides to Kb and they are both 8 amino acid residues in length, i.e., "from 8 to 14 amino acids", and the heteroclitic peptides were designed to bind to MHC with greater affinity than the target peptides without alteration of the immune recognition portion (especially column 1 on page 1554).

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

Applicant's comments regarding that they are in the process of obtaining a Katz declaration to remove Dyall et al as prior art is noted by the Examiner.

9. Claims 1, 2, 9 and 16 stand rejected under 35 U.S.C. 102(a) as being anticipated by Huard et al (Int. Immunol. 9(11), 1997, 1701-1701) as evidenced by admissions in the instant specification on page 13 at lines 20-23.

Huard et al teach a method for inducing a cellular immune response in Kbm8-bearing mice to a heteroclitic peptide SEIEFARL (i.e., the therapeutic antigen) (hsV-8), which is a variant of peptide SSIEFARL (i.e., the target peptide). The target peptide SSIEFARL cannot elicit a CTL response in Kbm8-bearing mice (especially Table 1 on page 1705). The heteroclitic peptide bound with greater affinity than the target peptide to Kbm8 and it is 8 amino acid residues in length, i.e., "from 8 to 14 amino acids", and the heteroclitic peptide was designed to bind to MHC with greater affinity than the target peptide without alteration of the immune recognition portion and it induced an immune response (i.e., "immune recognition domain binds to a cytotoxic T cell"). Huard et al further teach that SSIEFARL (i.e., the therapeutic antigen) binds to MHC class I molecule Kb in Kb-bearing B6 mice and further teaches a method for inducing an immune response using the said peptide in Kb-bearing mice. Huard et al teach that the said peptide does not induce an immune response in Kbm8 bearing mice, whereas SEIEFARL (i.e., the target peptide) does.

The admissions in the specification on page 13 at lines 20-23 is that the SSI (i.e., SSIEFARL) peptide is a heteroclitic vaccine peptide and that SEI (i.e., SEIEFARL) is the parental peptide [or "target" peptide] in B6 mice.

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

It is Applicant's position beginning on page 7 and continuing on to page 8 of the said amendment that the art reference does not teach a method of inducing a cellular immune response to HSV glycoprotein B peptide by administration of SSIEFARL and that the reference does not show immunization, that the reference teaches peptide binding only. It is the Applicant's further position that the instant rejection seems to be arguing at different times that both SSIEFARL and SEIEFARL are the heteroclitic peptide.

It is the Examiner's position that the art reference teaches recognition of the heteroclitic peptides by CTL (especially last page of the article). It is the Examiner's further position that depending upon the strain of mouse used, Kbm-8 or Kb, i.e., the mammalian subject, the same peptide is heteroclitic in one strain and the target peptide in another strain, and visa versa, as enunciated supra in the instant rejection.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 2 and 4 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dyall et al (J. Exp. Med 188(9), 1553-1561, 11/2/98, IDS reference) in view of Anderson et al (J. Exp. Med. 174, 8/1991, 489-492, IDS reference) and Yewdell et al (J. Immunol. 152, 1994, 1163-1170, IDS reference).

Dyall et al teach a method for inducing a cellular immune response to a heteroclitic peptide SSIEFARL (i.e., the therapeutic antigen) (hsV-8), which is a variant of peptide SEIEFARL (i.e., the target antigen) which binds poorly to the murine class I MHC molecule H-2Kb and which due to poor binding cannot elicit a CTL response in Kb-bearing B6 mice (especially paragraph spanning columns 1 and 2 on page 1555) and also to a heteroclitic variant TAYRYHLL of peptide TWHRYHLL from gp75 which displayed poor binding similar to the SEIEFARL peptide (especially page 1557). Both heteroclitic peptides bound with greater affinity than the target peptides to Kb and they are both 8 amino acid residues in length, i.e., "from 8 to 14 amino acids", and the heteroclitic peptides were designed to bind to MHC with greater affinity than the target peptides without alteration of the immune recognition portion (especially column 1 on page 1554). Dyall et al teach fusion proteins encoded by ERIS (i.e., ER sorting/ trafficking signal)-containing minigenes have been shown to insert the attached class I binding peptides into the ER for presentation by Class I MHC (especially column 1 on page 1556).

Dyall et al do not teach the claimed method wherein the therapeutic antigen further comprises an ER trafficking signal.

Anderson et al teach a peptide preceeded by an endoplasmic reticulum translocation signal (i.e., ER sorting/trafficking signal) and the importance of peptide transport into the ER for expression of class I MHC-peptide complexes for induction of immune response.

Yewdell et al teach antigenic peptides carboxy terminal to an ER insertion sequence and the importance of the ER insertion sequence in delivering the peptide to the ER for peptide/MHC class I expression at the cell surface.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a heteroclitic peptide connected to an ER sorting/trafficking signal as taught by Anderson et al or Yewdell et al or Dyall et al to be used in the method of Dyall et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more efficiently induce an immune response to the heteroclitic peptide in the method of Dyall et al given the teachings of Anderson et al and Yewdell et al of the importance of peptide transport into the ER for expression of class I MHC-peptide complexes at the cell surface.

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on page 8.

Applicant's comment that they are preparing a declaration that Dyall et al is not prior art is noted by the Examiner.

12. Claims 1-4, 9, 11 and 12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/29193 (IDS reference) in view of Anderson et al (J. Exp. Med. 174, 8/1991, 489-492, IDS reference) and Yewdell et al (J. Immunol. 152, 1994, 1163-1170, IDS reference).

WO 95/29193 teaches a method of inducing an immune response by administering heteroclitic peptides from tumor antigens, including gp100, altered to improve peptide MHC class I (including HLA-A2.1) binding affinity and to render the peptide capable of inducing an immune response (i.e., "immune recognition domain binds to a cytotoxic T cell") whereas it had not been immunogenic prior to alteration (especially introduction and last paragraph on page 302). The peptides are 8 amino acid residues in length, i.e., "from 8 to 14 amino acids". WO 95/29193 teaches that some of the wild-type peptides induce a partial response or no response at all as measured by recognition by HLA-A2 restricted TIL, i.e., are "weakly immunogenic" (especially Tables, Table 11). The peptides taught by WO 95/29193 are "from 8 to 14 amino acids" in length.

WO 95/29193 does not teach the claimed method wherein the therapeutic antigen further comprises an ER trafficking signal.

Anderson et al teach a peptide preceeded by an endoplasmic reticulum translocation signal (i.e., ER sorting/trafficking signal) and the importance of peptide transport into the ER for expression of class I MHC-peptide complexes for induction of immune response.

Yewdell et al teach antigenic peptides carboxy terminal to an ER insertion sequence and the importance of the ER insertion sequence in delivering the peptide to the ER for peptide/MHC class I expression at the cell surface.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a heteroclitic peptide connected to an ER sorting/trafficking signal as taught by Anderson et al or Yewdell et al to be used in the method of WO 95/29193.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more efficiently induce an immune response to the heteroclitic peptide in the method of WO 95/29193 given the teachings of Anderson et al and Yewdell et al of the importance of peptide transport into the ER for expression of class I MHC-peptide complexes

at the cell surface. Claim 12 is included in this rejection because gp100 is expressed in normal and tumor tissues.

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on page 8.

It is the Examiner's position with regard to Applicant's arguments pertaining to WO 95/29193 that the Examiner's arguments enunciated in item # 6 supra of this office action pertain to this rejection. It is the Examiner's further position that WO 95/29193 teaches recognition of heteroclitic peptides by TIL, i.e., CTL from tumor sites in vivo.

13. Claims 1-4, 9 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford et al Immunology 84(2), 1995, 298-303, IDS reference) in view of Anderson et al (J. Exp. Med. 174, 8/1991, 489-492, IDS reference) and Yewdell et al (J. Immunol. 152, 1994, 1163-1170, IDS reference).

Lipford et al teach a method of inducing an immune response by administering a heteroclitic peptide YIFAFRDL which was altered from HPV E6 peptide YDFAFRDL at position 2 to improve peptide MHC class I H-2Kb binding affinity, and to render it capable of inducing an immune response (i.e., "immune recognition domain binds to a cytotoxic T cell") whereas it had not been immunogenic prior to alteration (especially introduction and last paragraph on page 302). The peptides are 8 amino acid residues in length, i.e., "from 8 to 14 amino acids".

Lipford et al do not teach the claimed method wherein the therapeutic antigen further comprises an ER trafficking signal.

Anderson et al teach a peptide preceeded by an endoplasmic reticulum translocation signal (i.e., ER sorting/trafficking signal) and the importance of peptide transport into the ER for expression of class I MHC-peptide complexes for induction of immune response.

Yewdell et al teach antigenic peptides carboxy terminal to an ER insertion sequence and the importance of the ER insertion sequence in delivering the peptide to the ER for peptide/MHC class I expression at the cell surface.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a heteroclitic peptide connected to an ER sorting/trafficking signal as taught by Anderson et al or Yewdell et al to be used in the method of Lipford et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more efficiently induce an immune response to the heteroclitic peptide in the method of Lipford et al given the teachings of Anderson et al and Yewdell et al of the importance of peptide transport into the ER for expression of class I MHC-peptide complexes at the cell surface.

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on page 8.

It is the Examiner's position with regard to Applicant's arguments pertaining to Lipford et al that the Examiner's arguments enunciated in item # 7 supra of this office action pertain to this rejection.

14. Claims 1, 2, 9 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huard et al (Int. Immunol. 9(11), 1997, 1701-1701) in view of admissions in the specification on page 13 at lines 20-23.

Huard et al teach a method for inducing a cellular immune response to a heteroclitic peptide SEIEFARL (i.e., the therapeutic antigen) (hsV-8), which is a variant of peptide SSIEFARL (i.e., the target antigen) cannot elicit a CTL response in Kbm8-bearing mice (especially Table 1 on page 1705). The heteroclitic peptide bound with greater affinity than the target peptide to Kbm8 and it is 8 amino acid residues in length, i.e., "from 8 to 14 amino acids", and the heteroclitic peptide was designed to bind to MHC with greater affinity than the target peptide without alteration of the immune recognition portion and it induced an immune response (i.e., "immune recognition domain binds to a cytotoxic T cell"). Huard et al further teach that SSIEFARL binds to MHC class I molecule Kb in Kb-bearing mice and induces an immune response. It does not bind to induce an immune response in Kbm8 bearing mice, whereas SEIEFARL does.

Huard et al do not teach a method wherein the method for inducing a cellular immune response comprises administration of a therapeutic antigen that is SSIEFARL (SEQ ID NO: 10 of the instant application).

The admissions in the specification on page 13 at lines 20-23 is that the SSI (i.e., SSIEFARL) peptide is a heteroclitic vaccine peptide and that SEI (i.e., SEIEFARL) is the parental peptide in B6 mice.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have induced an immune response similar to the response taught by Huard et al in Kbm8-bearing mice by altering the method of Huard et al to use Kb-bearing

mice and to have substituted the peptide SSIEFARL for SEIEFARL, i.e., to have used the peptide SSIEFARL as the therapeutic antigen.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to induce an immune response to HSV in Kb-bearing mice.

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on page 8.

It is the Examiner's position with regard to Applicant's arguments pertaining to Huard et al that the Examiner's arguments enunciated in item # 9 supra of this office action pertain to this rejection.

15. Claims 1-4, 9 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huard et al (Int. Immunol. 9(11), 1997, 1701-1701) in view of admissions in the specification on page 13 at lines 20-23 and further in view of Anderson et al (J. Exp. Med. 174, 8/1991, 489-492, IDS reference) and Yewdell et al (J. Immunol. 152, 1994, 1163-1170, IDS reference).

Huard et al teach a method for inducing a cellular immune response in Kbm8-bearing mice to a heteroclitic peptide SEIEFARL (i.e., the therapeutic antigen) (hsV-8), which is a variant of peptide SSIEFARL (i.e., the target peptide). The target peptide SSIEFARL cannot elicit a CTL response in Kbm8-bearing mice (especially Table 1 on page 1705). The heteroclitic peptide bound with greater affinity than the target peptide to Kbm8 and it is 8 amino acid residues in length, i.e., "from 8 to 14 amino acids", and the heteroclitic peptide was designed to bind to MHC with greater affinity than the target peptide without alteration of the immune recognition portion and it induced an immune response (i.e., "immune recognition domain binds to a cytotoxic T cell"). Huard et al further teach that SSIEFARL (i.e., the therapeutic antigen) binds to MHC class I molecule Kb in Kb-bearing B6 mice and further teaches a method for inducing an immune response using the said peptide in Kb-bearing mice. Huard et al teach that the said peptide does not induce an immune response in Kbm8 bearing mice, whereas SEIEFARL (i.e., the target peptide) does.

The Huard not teach the claimed method wherein the therapeutic antigen further comprises an ER trafficking signal and Huard et al do not teach that the SEIEFARL peptide is the parental peptide in B6 mice.

The admissions in the specification on page 13 at lines 20-23 is that the SSI (i.e., SSIEFARL) peptide is a heteroclitic vaccine peptide and that SEI (i.e., SEIEFARL) is the parental peptide [or "target" peptide] in B6 mice.

Anderson et al teach a peptide preceeded by an endoplasmic reticulum translocation signal (i.e., ER sorting/trafficking signal) and the importance of peptide transport into the ER for expression of class I MHC-peptide complexes for induction of immune response.

Yewdell et al teach antigenic peptides carboxy terminal to an ER insertion sequence and the importance of the ER insertion sequence in delivering the peptide to the ER for peptide/MHC class I expression at the cell surface.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a heteroclitic peptide connected to an ER sorting/trafficking signal as taught by Anderson et al or Yewdell et al to be used in the method of the combination of Huard et al given the above-cited admissions in the instant specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more efficiently induce an immune response to the heteroclitic peptide in the method of the combination of Huard et al given the teachings of Anderson et al and Yewdell et al of the importance of peptide transport into the ER for expression of class I MHC-peptide complexes at the cell surface.

Applicant's arguments in the amendment filed 12/4/03 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on page 8.

It is the Examiner's position with regard to Applicant's arguments pertaining to Huard et al that the Examiner's arguments enunciated in item # 9 supra of this office action pertain to this rejection. It is the Examiner's further position with regard to Applicant's argument that the SEI peptide described by Huard as having CTL recognition in Kbm-bearing mice was found to be ineffective in providing anti-tumor benefits in the present application on page 14 is not in conflict with Huard et al because Huard et al teach non-reactivity in B6 mice and so does the instant specification on page 14.

16. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 31, 2004

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